Effect of Olanzapine, Risperidone, and Haloperidol Treatment on Weight and Body Mass Index in First-Episode Schizophrenia Patients in India: A Randomized, Double-Blind, Controlled, Prospective Study

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Objective: The presence of obesity and increases in body mass are important risk factors for cardiovascular disease and diabetes. This study examined the effects of olanzapine, risperidone, and haloperidol on weight, body mass index (BMI), and development of obesity in a drug-naive population compared with a matched healthy control group.

Method: Consecutive patients during the period from June through October 2006 with DSM-IV schizophrenia at our referral psychiatric hospital were recruited for an extensive prospective study that included anthropometric measures of weight, waist circumference, waist-hip ratio, and BMI. Subjects were randomly assigned to receive haloperidol, olanzapine, or risperidone and compared with a matched healthy control group. The prevalence of obesity, which was the main outcome measure, was assessed on the basis of 2 criteria: revised World Health Organization (WHO) definition for Asians and criteria of the International Diabetes Federation (IDF). Inclusions started in June 2006, and patients were followed for a period of 6 weeks.

Results: The analysis of 66 patients showed a prevalence of overweight (WHO criteria) at 22.7% and obesity at 31.8% (IDF criteria). The prevalence of obesity (IDF criteria) in our patients is over 30 times as high as that of the matched healthy control group ($p < .001$). Subjects in the olanzapine group had the greatest weight gain at 5.1 kg, followed by risperidone at 4.1 kg and haloperidol at 2.8 kg.

Conclusions: Obesity is highly prevalent among patients treated with atypical antipsychotics for schizophrenia. Assessment and monitoring of obesity along with preventive and curative measures should be part of the clinical management of patients treated with antipsychotics.

Trial Registration: ClinicalTrials.gov, NCT00534183, www.clinicaltrials.gov.

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Obesity, especially the presence of central obesity, is a chronic condition characterized by an excess of body fat[1] that is linked to several diseases. Several epidemiologic and metabolic studies[1–3] conducted over the last 15 years have confirmed the notion that a high proportion of abdominal fat (central obesity) is a major risk factor for coronary heart disease, type 2 diabetes mellitus, and related mortality. Central obesity is now positively associated with type 2 diabetes, coronary heart disease, hypertension, gall bladder disease, certain types of cancer, dyslipidemia, and insulin resistance.[3]

Several psychotropic medications have been known to increase weight, including conventional and atypical antipsychotics, tricyclic antidepressants, mirtazapine, lithium, sodium valproate, and gabapentin.[4] Atypical antipsychotics, which form an important therapeutic option for many individuals with schizophrenia and other psychoses, have been implicated in weight gain that is dependent on the particular drug and the individual patient. Weight gain occurs shortly after starting treatment but may plateau or even decrease after 1 year.[5]

Of all atypical antipsychotics, clozapine is reported to cause the greatest weight gains seen with any antipsychotic drug.[6] A synthesis of studies with clozapine has reported that patients taking clozapine gain a mean of 6 to 7 kg over treatment periods ranging from 16 weeks to 3 years.[7–10]

Olanzapine is associated with significant weight gain of a magnitude comparable to that produced by clozapine.[11] Long-term data indicate that olanzapine is associ-

ated with the greatest weight gain over 1 year of treatment. Weight gain with olanzapine at the commonly used dose of 15 mg/day may exceed 10 kg during the first year of treatment.[11] Weiden et al.[12] reported that "problematic" weight gain can occur with just 6 weeks of treatment. Beasley et al.[13] reported a clinically significant weight gain in 41% of patients from combined studies. This effect is not limited to just schizophrenia but extends to even mood disorders. A recent study of olanzapine with or without fluoxetine in treatment-resistant depression reported a weight gain of 6.07 kg with olanzapine alone over 8 weeks.[14]

Risperidone, on the other hand, is associated with modest weight gain that is not dose related. Most studies have reported a mean weight gain of about 2 to 2.5 kg over a treatment period ranging from 8 weeks to 1 year[15–17]; however, negative studies have also been reported.[18] Although risperidone is generally believed to cause only modest changes in weight, 2 recent cases have suggested that may not be so.[19,20]

Limited data exist on the effect of typical antipsychotics on weight. Haloperidol has generally been shown to cause less weight gain than the atypicals and chlorpromazine. Sanger et al.[21] reported weight gain of 0.5 kg at 6 weeks, and Kinon et al.[22] reported an increase of 0.69 kg after 1.15 years. Csernansky et al.[17] has reported the opposite with a decrease of 0.73 kg with haloperidol treatment over 1 year. Therefore, the consensus through a meta-analysis[6] is that the mean weight gain is greatest with clozapine at 4.45 kg, followed by olanzapine at 4.15 kg, risperidone at 2.10 kg, and haloperidol at 1.08 kg. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study observed much more weight gain (body mass index [BMI] increase of > 7% of baseline) with olanzapine—30% within the follow-up period (up to 1 year)—than with other agents (quetiapine, 16%; risperidone, 14%; perphenazine, 12%; ziprasidone, 7%).[23] Another comprehensive review that estimated the naturalistic impact of second-generation antipsychotics on weight gain[10] reported that olanzapine followed by risperidone had a greater propensity to cause weight gain than the first-generation antipsychotics.

However, the other side of the argument also merits attention. It has been suggested that schizophrenia itself is associated with increased weight.[24] Schizophrenia, before the advent of pharmacotherapy, had been associated with obesity.[25,26] Thakore et al.[27] measured visceral fat distribution using computed tomography in 15 patients with schizophrenia and, after matching them with healthy controls, found that patients with schizophrenia had a higher mean BMI than the control group. This study is limited by the mixed nature of its sample with 7 drug-naive patients and 8 drug-free patients. Other researchers have argued, however, that the unhealthy diets, sedentary lifestyles, and substance use present in patients with schizophrenia may be responsible for weight gain.[28]

Is it therefore possible that a mechanism other than medication might be responsible for such findings? Unfortunately, the numerous articles that argue about the effects of antipsychotics have several methodological limitations. These include the limited number of randomized controlled trials; the cross-sectional design in most studies, which precludes the identification of causal relationships; the variation in outcome measures used to summarize weight change; the effect of other medications that can cause weight gain such as antidepressants and mood stabilizers; and the presence of other confounders such as prior antipsychotic treatment and the impact of baseline body mass index. Such limitations can be overcome by prospective studies on first-episode schizophrenia patients, who, being drug naive, avoid the confounding effect of prior antipsychotic treatment. To date, there have been only 3 such studies. Lieberman et al.[29] reported the mean weight increase with chlorpromazine as 6.5 kg and with clozapine as 9.9 kg. However, weight was not systematically measured in this study, which lasted 135 weeks. Zhang et al.[30] reported a mean weight gain of 4.64 kg with chlorpromazine and risperidone but did not isolate the effect of each antipsychotic. In the SOHO (Schizophrenia Outpatient Health Outcomes) study, Novick et al.[31] found that olanzapine-treated patients gained more weight (4.3 kg, SD = 6.5 kg) after 24 months of treatment compared with patients treated with risperidone (3.6 kg, SD = 5.2 kg), other atypicals (2.5 kg, SD = 8.33 kg), and typicals (1.75 kg, SD = 4.8 kg).

Our study attempts to answer the question of whether antipsychotic treatment causes weight gain in schizophrenia patients by accounting for these confounding variables. We aimed to study the effects of the antipsychotics olanzapine, risperidone, and haloperidol on weight and BMI and development of obesity in a drug-naive population compared with a matched healthy control group.

METHOD

All consecutive patients during the period from June through October 2006 with a DSM-IV diagnosis of schizophrenia in Central Institute of Psychiatry, Ranchi, India, which is a referral psychiatric institute, were asked to participate in an extensive screening and prospective follow-up study of metabolic parameters after obtaining written informed consent as per the Institutional Review Board for Biomedical Research. The prospective inclusions started in June 2006 and patients were followed up for a period of 6 weeks.

Patients with other psychiatric comorbidity, history of severe physical illness, alcohol and substance abuse or dependence, and history of preexisting diabetes or hypertension or family history of hypertension or diabetes were excluded from the study at the initial screening.

Table 1. Baseline Comparison of Control Group With Combined Treatment Groups (olanzapine, risperidone, and haloperidol)

Variable	Control Group (N = 51)	Treatment Groups (N = 66)	Statistic	Degrees of Freedom	Significance (p value)
Age, mean ± SD (y)	27.5 ± 5.9	26.7 ± 6.3	t = 0.6930	115	.490
Gender, N (%)					
Male	30 (58.8)	31 (47)	χ^2 = 1.620	1	.263
Female	21 (41.2)	35 (53)			
Waist circumference, mean ± SD (cm)					
All	72.3 ± 4.5	73.0 ± 8.6	t = 0.537	115	.592
Male (reference < 94 cm)	74.6 ± 3.3	74.6 ± 9.5	t = 0.007	59	.994
Female (reference < 80 cm)	69.0 ± 4.0	71.6 ± 7.6	t = 1.427	54	.159
Weight, mean ± SD (kg)					
All	50.4 ± 4.3	48.3 ± 10.5	t = 1.325	115	.188
Male	52.0 ± 2.3	52.8 ± 10.9	t = 0.363	59	.718
Female	48.0 ± 5.2	44.3 ± 8.4	t = 1.779	54	.081
Waist-hip ratio, mean[a]					
All	0.90	0.86	t = 4.039	115	< .001
Male (reference < 0.90)	0.91	0.88	t = 2.574	59	.013
Female (reference < 0.85)	0.88	0.83	t = 2.834	54	.006
Body mass index, mean ± SD (kg/m^2)					
All (reference < 23 kg/m^2)	19.5 ± 2.3	19.2 ± 3.2	t = 0.076	115	.538
Male	19.0 ± 1.2	19.3 ± 4.0	t = 0.372	59	.711
Female	20.3 ± 3.2	19.1 ± 2.4	t = 1.510	54	.137

[a]Standard deviations not shown because the values are too small.

Patients included in the study were randomly assigned to receive risperidone, olanzapine, or haloperidol. No other drugs, which could potentially influence weight, were allowed for the observation period. All patients received the same diet and were subjected to the same daily exercise regimen (as inpatients), therefore controlling for these confounding variables. A healthy control group matched in terms of gender, age, exercise and diet (by basal metabolic rate),[32] and other confounding variables such as race and socioeconomic status was also chosen.

At baseline, anthropometric measurements of weight, waist circumference, BMI, and waist-hip ratio were recorded after an overnight fast to maintain uniformity. Using a tape measure, with the subject standing, the waist was measured as the narrowest circumference between the lower costal margin and the iliac crest. The hip was the maximum circumference at the level of the femoral trochanters. The BMI was calculated as weight in kg divided by the square of height in meters. These measurements were repeated at 2, 4, and 6 weeks (endpoint). All assessments were performed by a single investigator blind to diagnosis and medication prescribed. According to World Health Organization (WHO) Expert Consultation for Asian Population,[33] obesity was defined as BMI > 27 kg/m^2 and overweight, as BMI of 23 through 27 kg/m^2. According to the International Diabetes Federation (IDF) criteria, obesity was defined as waist circumference > 80 cm for women and > 94 cm for men.

Statistical Analysis

Descriptive statistics were computed for clinical variables, and the differences across the timeline were assessed by a multivariate repeated measures test. The development of obesity defined by BMI, waist-hip ratio, or waist circumference was assessed using χ^2 test.

This study was performed in accordance with the broad framework of the Declaration of Helsinki[34] and was approved by the institutional ethical committee.

RESULTS

The sample size of the present study was 66, of which 40 (60.6%) were diagnosed with paranoid schizophrenia and 26 (39.4%) with undifferentiated schizophrenia. The mean ± SD duration of untreated illness was 13.4 ± 11.5 months. The mean age of the subjects was 26.7 ± 6.4 years. Further, 29 (43.9%) of the subjects were on stable dosages of olanzapine (mean = 17.0 ± 5.0 mg), 22 (33.3%) were taking risperidone (mean = 4.5 ± 1.2 mg), and 15 (22.7%) were taking haloperidol (mean = 15.6 ± 2.6 mg).

Table 1 presents the comparison of sociodemographic and anthropometric measurements between the combined treatment groups and control group. There were no significant differences between the groups in age, gender, and other anthropometric measurements, with the exception of waist-hip ratio.

Table 2 presents the comparison of different variables from baseline to endpoint across all groups. Multivariate analysis was done between the 3 treatment groups (olanzapine, risperidone, and haloperidol) and the control group. There was a statistically significant increase in waist circumference ($p < .001$), weight ($p < .001$), waist-hip ratio ($p < .001$), and BMI ($p < .001$) from baseline to endpoint between the groups. This significance is present even when the data are compared across both genders, male subjects only, and female subjects only.

Table 2. Comparison of Anthropometric Measurements From Baseline to Endpoint Between Treatment Groups

Treatment Group	Waist Circumference, mean (SD), cm			Weight, mean (SD), kg			Waist-Hip Ratio, mean[a]			Body Mass Index, mean (SD), kg/m^2		
	Baseline	Endpoint	F value (df = 3)*	Baseline	Endpoint	F value (df = 3)*	Baseline	Endpoint	F value (df = 3)*	Baseline	Endpoint	F value (df = 3)*
Control												
All (N = 51)	72.3 (4.5)	72.6 (4.5)	52.2	50.4 (4.3)	50.4 (4.2)	33.9	0.90	0.90	49.3	19.5 (2.3)	19.5 (2.4)	29.0
Male (N = 30)	74.4 (3.3)	74.6 (3.5)	82.3	52.0 (2.3)	52.0 (2.0)	30.8	0.91	0.91	69.2	19.0 (1.2)	19.0 (1.3)	30.4
Female (N = 21)	69.0 (4.0)	69.7 (4.2)	18.1	48.0 (5.2)	48.0 (5.3)	10.2	0.88	0.89	16.6	20.3 (3.2)	20.3 (3.3)	9.3
Combined												
All (N = 66)	73.0 (8.6)	79.2 (8.8)		48.3 (10.5)	52.5 (10.4)		0.86	0.93		19.2 (3.2)	20.9 (3.4)	
Male (N = 31)	74.6 (9.5)	79.3 (9.9)		52.8 (10.9)	56.9 (10.9)		0.88	0.94		19.3 (4.0)	20.8 (4.0)	
Female (N = 35)	71.6 (7.6)	79.0 (7.9)		44.3 (8.4)	48.6 (8.3)		0.83	0.92		19.1 (2.4)	21.1 (2.8)	
Olanzapine												
All (N = 29)	72.3 (8.9)	80.7 (8.4)		45.6 (11.5)	50.7 (11.4)		0.83	0.93		19.0 (3.9)	21.2 (4.0)	
Male (N = 11)	74.7 (10.7)	81.2 (11.0)		53.2 (14.0)	58.7 (14.0)		0.88	0.95		19.2 (5.6)	21.2 (5.6)	
Female (N = 18)	70.7 (7.4)	80.5 (6.6)		41.0 (6.4)	45.7 (5.7)		0.80	0.91		18.9 (2.7)	21.2 (2.9)	
Risperidone												
All (N = 22)	73.9 (10.2)	79.3 (10.9)		48.7 (10.8)	52.8 (11.1)		0.88	0.95		19.5 (3.3)	21.1 (3.5)	
Male (N = 10)	75.1 (11.6)	80.0 (11.7)		51.7 (11.8)	55.5 (11.7)		0.90	0.96		19.5 (4.1)	20.9 (4.0)	
Female (N = 12)	73.0 (9.3)	78.6 (10.6)		46.2 (9.7)	50.6 (10.5)		0.87	0.94		19.4 (2.6)	21.3 (3.2)	
Haloperidol												
All (N = 15)	73.1 (5.4)	76.0 (5.3)		52.8 (5.8)	55.6 (5.9)		0.87	0.90		19.2 (1.2)	20.2 (1.3)	
Male (N = 10)	74.0 (6.1)	76.6 (6.3)		53.4 (6.0)	56.2 (5.7)		0.87	0.91		19.2 (1.4)	20.2 (1.4)	
Female (N = 5)	71.4 (3.2)	74.8 (2.6)		51.8 (6.0)	54.4 (6.9)		0.85	0.89		19.2 (0.5)	20.1 (1.2)	

[a]Standard deviations are not shown because the values are too small.
*Significant at $p < .001$.

There is also a statistically nonsignificant trend in development of obesity defined as a BMI above 27 kg/m^2 at endpoint ($p = .078$; $\chi^2 = 6.808$) and significant increase in obesity by waist circumference ($p < .001$; $\chi^2 = 33.73$; Table 3). Further, there is also a significant increase in pre-obesity or overweight as defined by a BMI of 23 through 27 kg/m^2 ($p = .007$; $\chi^2 = 12.226$).

The olanzapine group had the greatest increase in waist circumference with a mean of 8.4 ± 4.2 cm, followed by the risperidone group at 5.3 ± 4.3 cm and the haloperidol group at 2.8 ± 1.0 cm. The olanzapine group also gained the greatest amount of weight gain with a mean of 5.0 ± 3.2 kg, followed by risperidone at 4.1 ± 2.4 kg and haloperidol at 2.7 ± 3.1 kg. For overall BMI, the olanzapine group again gained the most at 2.1 ± 1.5 kg/m^2, followed by risperidone at 1.6 ± 1.2 kg/m^2 and haloperidol at 1 ± 1.17 kg/m^2. Female subjects appeared to gain more in all parameters than males: waist circumference, 7.4 ± 5.3 cm compared with 4.7 ± 2.2 cm for males; weight, 4.3 ± 3.5 kg compared with 4.0 ± 2.4 kg, respectively; and BMI, 1.9 ± 1.7 kg/m^2 compared with 1.4 ± 0.8 kg/m^2, respectively.

Treatment-emergent obesity was present in 10.3% of subjects in the olanzapine group, 9.1% in the risperidone group, and none in the haloperidol group by the WHO definition and in 44.8% of those in the olanzapine group, 36.4% in the risperidone group, and none in the haloperidol group by the IDF definition.

DISCUSSION

There have been increasing concerns about the overall health care of patients with schizophrenia during the recent decade. Other than the devastating consequences that the illness poses for the individual, patients with schizophrenia also suffer increased medical morbidity and mortality compared with the general population, with a large body of literature documenting both increased prevalence and severity of medical disorders and undertreatment of common medical conditions.[35,36] Unfortunately, research of late has also led to the realization that atypical antipsychotics may be contributors to the medical morbidity of schizophrenia. It has also been recognized that there are differential effects among these agents on metabolic outcomes, with clozapine, olanzapine, and quetiapine associated with greater adverse effects on weight and other metabolic parameters than risperidone, ziprasidone, or haloperidol.[6,10]

Our study on the prevalence of treatment-emergent obesity in drug-naive patients diagnosed with schizophrenia is the largest study on an Indian

Table 3. Comparison of Prevalence of Overweight or Obesity at Endpoint Between Treatment Groups

Criterion	Control Group (N = 51)	Treatment Group				χ^2	Significance (p)
		Combined (N = 66)	Olanzapine (N = 29)	Risperidone (N = 22)	Haloperidol (N = 15)		
World Health Organization, %							
Overweight (body mass index, 23 to ≤ 27 kg/m^2)	3.9	22.7	27.6	27.3	6.7	12.226	.007
Obese (body mass index > 27 kg/m^2)	0	7.6	10.3	9.1	0	6.808	.078
International Diabetes Foundation, %							
Obese (Waist circumference: female, > 80 cm; male, > 94 cm)	0	31.8	44.8	36.4	0	33.73	< .001

population as of today. By its prospective design, this study has attempted to answer many of the questions that previous studies posed and has controlled for confounding variables by both matching and randomization. We chose the 6-week period as it represents an often-followed time frame in clinical practice to determine treatment outcome and decide on treatment discontinuation. Also, the rate of weight gain, as described with clozapine, is such that the increase between 6 weeks and 6 months has been found to be equivalent in magnitude to that between baseline and 6 weeks.[37] The results of this study reveal that prevalence of treatment-emergent obesity within 6 weeks of treatment with the atypical antipsychotics olanzapine and risperidone is significant when compared with that of haloperidol and a control group, although the difference between olanzapine and risperidone is small.

Further, olanzapine is associated with a mean weight gain of 5.0 kg, followed by risperidone at 4.1 kg and haloperidol at 2.7 kg, findings similar to those of the CATIE study[23] and the meta-analytic review.[10] Olanzapine is also associated with greater central adiposity or abdominal fat with an increase in mean waist circumference of 8.4 cm, followed by risperidone at 5.3 cm and haloperidol at 2.8 cm. However, this increase is even more obvious in female subjects, as they gained a mean of 7.4 cm compared with male subjects who gained a mean of 4.7 cm. This weight gain represents an additional morbidity, as weight gain has important effects on reproduction and breast cancer. Once again, olanzapine is particularly obesitogenic compared with risperidone or haloperidol. This rapid increase in waist circumference is a matter of grave concern, as Indians are particularly sensitive to gaining weight around the middle and developing diabetes mellitus as well as cardiovascular disease.[38] This tendency has prompted WHO to revise their criterion for healthy BMI to 18.5 to 22 kg/m^2 for Asian populations and for overweight or pre-obesity to at least 23 and through 27 kg/m^2.[33] Since nearly 27% of our study population in both the olanzapine and risperidone groups were considered pre-obese, greater caution should be used when prescribing these medications.

Weight gain is one of the most prominent difficulties associated with the use of atypical antipsychotic drugs, since a weight change of 5% or 5 kg is considered significant. This effect is an important consideration in the selection of pharmacologic therapy, as it may lead to decreased quality of life,[39] poor adherence to medication, increased relapse rates,[40] and increasing mortality from all causes.[41] These are in addition to the immediate concerns of patients regarding weight gain, which are poor physical function, discomfort in public places, poor self-esteem, and problems with sexual performance.[42]

The need of the hour is intensive screening to recognize the risk factors for weight gain and to launch preventive and curative measures. Lifestyle changes, smoking cessation, regular exercise, and reduction of obesity by dietary interventions should be undertaken aggressively. Early monitoring of patients taking atypical antipsychotics can possibly play an important role in early detection and hence prevention of development of obesity. It is recommended that clinicians should consider switching patients to a medication that is less likely to cause weight gain before clinically significant gains occur. Although haloperidol use is limited by long-term effects of tardive dyskinesia, we believe that the development of significant weight gain as seen with both olanzapine and risperidone should prompt the careful selection of pharmacotherapy after weighing the risks and benefits and explaining all possible consequences to the patient. The most important lesson to be learned, however, is that weight changes may be the new "tardive dyskinesia" of second-generation antipsychotics.

Drug names: clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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